UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

CELSIS IN VITRO, INC. a Maryland Corporation, Plaintiff, v. CELLZDIRECT, INC., a Delaware Corporation and wholly-owned subsidiary of INVITROGEN CORPORATION; and INVITROGEN CORPORATION, a Delaware Corporation. Defendants.	Case No. 1:10-cv-004053 Judge Milton I. Shadur Magistrate Judge Martin C. Ashman

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I. INTRODUCTION

CellzDirect and Invitrogen (collectively "LTC") have shown that LTC's method does not, in fact, infringe the '929 patent. Furthermore, LTC has raised substantial questions regarding the invalidity of the '929 patent in light of its failure to satisfy the written description requirement and its obviousness. Moreover, LTC has shown that Celsis's inequitable conduct should bar enforcement of the patent. Finally, the equities weigh against a preliminary injunction – Celsis's claimed harm is monetary in nature, and the public interest favors maintaining the availability of LTC's pooled human hepatocyte products for pharmaceutical research.

II. ARGUMENT

A. THERE IS A SUBSTANTIAL QUESTION REGARDING NON-INFRINGEMENT OF THE '929 PATENT.

Celsis has fallen short of meeting its burden of showing a likelihood of success on its infringement claims at trial for at least two fundamental reasons. First, LTC does not use "density gradient fractionation," as that term is properly construed, between the first thaw and second freeze in preparing its pooled human hepatocyte products. Second, even if the term "density gradient fractionation" is construed to include LTC's low speed centrifugation step between the first thaw and second freeze, then LTC also uses a "density gradient step" after the second thaw.

As a prefatory matter, Celsis has not presented any evidence that it or its experts actually tested or performed the accused processes in order to validate Dr. Strom's conjecture about LTC's method. Celsis asks the Court to shut down a substantial part of CellzDirect's business; yet Celsis did not even bother to perform the two short centrifugation steps that are central to Celsis's infringement case in order to determine whether a density gradient is in fact formed

under the LTC method. This absence of proof precludes Celsis from meeting its burden to prove that every limitation in Celsis's claims, as properly construed, is met by LTC's accused methods. *See, e.g., Intellicall, Inc. v. Phonometrics, Inc*., 952 F.2d 1384, 1388-89, 21 U.S.P.Q.2d 1383, 1387 (Fed.Cir 1992); *see also Abbott Labs. v. Baxter Healthcare Corp.*, 660 F. Supp. 2d 882, 888-89 (N.D. Ill. 2009) (noting that a plaintiff had not proven infringement because it failed to conduct experiments to establish defendant's infringement); *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d 381, 443 (S.D.N.Y. 2007) (holding that a conclusory statement regarding defendants' alleged infringement failed to prove infringement).

Celsis's failure to test is an acknowledgement of the dilemma its infringement theory faces. To prevail on its infringement claims, Celsis must show that the LTC method uses "density gradient fractionation" between the first thaw and second freeze, but does not require a "density gradient" step after the second thaw. Celsis has not – indeed, cannot – show that both limitations are met. Celsis contends that the short, low-speed centrifugation step used between the first and second thaw produces a "density gradient." However, under a proper construction of "density gradient," it does not. A long, high-speed centrifugation is required to form a density gradient. (JX 37 **(**Kreamer) at 202.) But even if Celsis's assertion were correct, then the short, low-speed centrifugation step LTC uses after the second thaw would also necessarily produce a "density gradient." As described in LTC's thawing protocol, this step is a requirement in LTC's method to obtain hepatocytes of high viability. (DX 3; *see also* JX 17.) Celsis cannot have it both ways – on the one hand, allege the first centrifugation step produces a density gradient, and on the other, contend that the second centrifugation step does not.

1. LTC Does Not Use "Density Gradient Fractionation" Between the First Thaw and Second Freeze Under a Proper Construction of That Term.

LTC's process for making its pooled cryopreserved human hepatocyte products does not

include density gradient fractionation between the first thaw and second freeze as required by Step (A) of Claim 1 and a proper construction of Claim 10.[1] The plain and ordinary meaning of "density gradient fractionation" to one of ordinary skill in the art[2] is "fractionation in a density gradient wherein the fractionation is based on no property other than density." (*See* JX 37 (Kreamer) at 202.) *See also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (*en banc*) (where the ordinary meaning of claim language as understood by a person of skill in the art is readily apparent, claim construction may involve "little more than the application of the widely accepted meaning of commonly understood words."). Dr. Strom agrees with LTC's construction: at the hearing, he testified that the specification does not disclose fractionation based on any property other than density alone (Tr. at 260:14-261:1), and the specification and prosecution history do not disclose any density-based separation procedure other than density gradient fractionation. (Tr. at 275:14-276:17.)[3]

As Markus Hunkeler (LTC's Director of Product Development and Marketing) testified, the accused process does not use "density gradient fractionation," but rather iso-density separation. (JX 8 (Supp. Hunkeler Decl. ¶ 7).) That is, LTC's method separates viable from

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[1] Although Claim 10 does not, like Claim 1, expressly require that the "multi-cryopreserved hepatocyte preparation" be prepared by "subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes," Claim 10 necessarily requires preparation of hepatocytes by density gradient fractionation. Celsis certainly understood that its claims required a density gradient step: it repeatedly argued during prosecution that "the claims require only that Percoll™ density gradient centrifugation is performed *prior* to refreezing." (JX 73 (Feb. 12, 2009 Amendment) at 17 (emphasis in original).) Celsis read the "density gradient fractionation" limitation into Claim 10 during prosecution in order to secure its allowance, as it had to for the claim to have any chance at validity.

[2] Dr. Gupta opined that a person of ordinary skill in the field of the '929 patent would have "moderate to high levels of skill." (Tr. at 443:2-13.) Dr. Gupta opined that such a person would have a bachelors degree in biology, pharmacology, or other relevant discipline, and one to three years of hands-on experience in cell isolation and purification techniques. (JX 34(Gupta Report) at ¶ 25.)

[3] In its memorandum in support of its motion for preliminary injunction, Celsis argued that "density gradient fractionation" should be construed to mean "a process for separating viable hepatocytes from non-viable hepatocytes based on their density." *See* Memo. at 10. Celsis's construction is nonsensical, because it reads "gradient" out of the limitation. Celsis's proposed construction is a blatant attempt to capture unclaimed density fractionation techniques that do not use a density gradient.

non-viable hepatocytes using a uniform (as opposed to a gradient) density solution (*id.*; *see* JX 37 (Kreamer) at 202). LTC's technique is expressly **not** covered by the asserted claims. Likewise, Dr. Li testified that Advanced Pharmaceutical Sciences' ("APS") process for making the accused products uses non-gradient "density fractionation (using Percoll centrifugation at low speed…)," and not "density gradient fractionation." (JX 9 (Li Decl. ¶ 6).)

In contrast, Celsis has based its infringement case on Dr. Strom's incorrect assumption that a density gradient is "always" formed during centrifugation no matter the duration, speed, or other conditions. (Tr. at 246:10-247:11.) Celsis and Dr. Strom offered no support for that supposed scientific "fact," and no proof that the centrifugation conditions actually used by LTC between the first thaw and second freeze result in a density gradient. Dr. Strom's conjecture cannot carry Celsis's infringement case.

2. If LTC Uses Density Gradient Fractionation After the First Thaw, Then It Also Uses A Density Gradient Step After Thawing Hepatocytes For A Second Time.

Even if Celsis were correct that the first centrifugation step produces a density gradient (which it does not), then LTC's second centrifugation step would also produce a density gradient. However, the asserted claims prohibit "a density gradient step after thawing the hepatocytes for the second time." (JX 1 ('929 Patent) at col. 20 lns. 15-16.) Because LTC performs the prohibited "density gradient step" (Step (C) of Claim 1), it does not infringe.

More specifically, after thawing the hepatocytes for a second time, LTC washes the hepatocytes to remove the toxic cryoprotectant that would otherwise kill or reduce viability of the cells. (Tr. at 566:3-569:12, 572:24-573:25, 647:22-649:14, 650:20-651:9; DX 3 at 3 (describing the "thaw, spin, resuspend" protocol).) That step requires pelleting the hepatocytes by short, low-speed centrifugation. (DX 3 at 3.) Dr. Strom testified that the precise

centrifugation conditions used by LTC in that centrifugation step produce a density gradient. (Tr. at 249:19-250:3; *see also* Tr. at 242:9-243:16.)

Realizing that under its unfounded interpretation of a density gradient that LTC performs a density gradient step after the second thaw, Celsis attempted to read into the claims requirements that the density gradient step "separate viable hepatocytes from non-viable hepatocytes" and "enhance the viability" of the hepatocytes. (Tr. at 661:20-663:3.) Celsis's attempt to re-write the "a density gradient step" limitation is without merit. A limitation cannot be introduced into narrow a claim term whose broader meaning from the claim language is unmistakable. *See Phillips*, 415 F.3d at 1323.[4]

B. THERE IS A SUBSTANTIAL QUESTION REGARDING THE VALIDITY OF THE '929 PATENT.

LTC has established that Celsis cannot show a likelihood of success on the merits because substantial questions exist regarding the validity of the '929 patent for at least two reasons: the asserted claims are invalid for failing to comply with the written description requirement, and are obvious in light of the prior art. *See Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1358 (Fed. Cir. 2001) (holding that a defendant need only establish vulnerability of the patent – not invalidity – to avoid a preliminary injunction).

1. The '929 Patent is Invalid for Lack of Written Description.

LTC's uncontroverted evidence establishes that Celsis's claims are invalid for failure to comply with the written description requirement because what Celsis has claimed as its invention is not disclosed in the specification. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*,

[4] Celsis's assertion that the term "a density gradient step" after Step (C) is the same as the term "a density gradient fractionation" in Step (A) is fundamentally flawed: the latter requires "fractionation" while the former does not, and the term "a density gradient step" is preceded by the indefinite article "a" signifying its introduction as a new element. If the "density gradient step" of Step (C) were a repeat of Step (A) then the definite article "said" would have been used.

598 F.3d 1336, 1347 (Fed. Cir. 2010) (*en banc*). Until faced with invalidating prior art during prosecution, Celsis had not contemplated the "no plating" requirement and "density gradient step" prohibition as part of its invention.[5] It is unsurprising, therefore, that no express or inherent descriptive support for these limitations exists in the originally filed application.

Celsis concedes that during prosecution the claims were amended to add limitations (1) requiring that "the hepatocytes are not plated between the first and second cryopreservations" and (2) prohibiting the performance of "a density gradient step after thawing the hepatocytes for the second time." (JX 68 (Aug. 15, 2008 Amendment) at 3 and 5.) Celsis further admits that these amendments were made to overcome the Examiner's obviousness rejection and secure allowance of the issued claims. (*See id*. at 10, 12.) Adding limitations to claims during prosecution is not *per se* impermissible; in fact, it is a standard part of the patent process. However, like any narrowing amendment, the limitations added by Celsis must have descriptive support in the original specification to satisfy the written description requirement. *E.g.*, *In re Huston*, 308 F.3d 1267, 1276-77, 64 U.S.P.Q.2d 1801 (Fed. Cir. 2002). In that respect, Celsis's suggestion that different disclosure obligations apply to negative limitations (which necessarily narrow claim scope) is without merit. (*See* Reply Brf. at 21-22.) This is because any claim containing a negative limitation that does not have basis in the original disclosure fails to comply with the written description requirement. *Ex parte Grasselli*, 231 U.S.P.Q. (BNA) 393, 394 (B.P.A.I. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984); *Ex parte Tao Xie*, 2008 WL 5232784, *2 (B.P.A.I. 2008) (unpublished); MPEP 2173.05(i).[6]

[5] The Court suggested at the hearing that the public is not "harmed by" the belated addition of these limitations so the lack of written support in the specification is excusable. (Tr. at 676.) Yet the public is harmed because Celsis is not entitled to a 20-year monopoly on an invention that is not adequately described to the public.

[6] Celsis's wrongly relies on *Ex parte Parks* as support for its assertion that the written description requirement is satisfied. In that case, the Board found that the person of ordinary skill in the art would have understood from the specification that the reaction was conducted "in the absence of a catalyst" because, according to unchallenged

Unfortunately for Celsis, neither of its negative limitations has support in the original disclosure.[7] It is plain from the face of the original application that the "no plating" requirement and "density gradient step" prohibition are not disclosed. Dr. Gupta testified that one of ordinary skill in the art would not find a description in the originally filed application (JX 57) of the claimed prohibition of plating between the first and second cryopreservations. (Tr. at 443:15-453:6.)

Celsis has failed to show that LTC's written description defense lacks merit. Celsis has not offered any evidence that a person of ordinary skill would recognize that either of the two added claim limitations was disclosed by the specification. Although Dr. Strom could have been called on to provide testimony on this topic, he did not offer any opinion regarding the adequacy of the written description. Celsis also did not offer any evidence that a person of ordinary skill in the art would recognize support for the prohibited "density gradient step." Celsis strained to find a description of the "not plated" requirement in the originally filed application, but could only point to the *lack of disclosure* of a "plating" step in Example 1's method. (Tr. at 761:5-10.)

Celsis's assertion that the specification's silence is a substitute for a written disclosure of the invention is at odds with legal precedent. The specification must have at least an affirmative indication that plating must be avoided. *E.g.*, *Ex parte Tao Xie* (concluding that the specification did not "expressly or implicitly support the negatively claimed feature" because the

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expert testimony, that person would have known that this type of reaction is conducted without a catalyst. *Ex parte Parks*, 30 U.S.P.Q.2d 1234, 1236 (B.P.A.I. 1994).

[7] A negatively claimed feature must be expressly or implicitly supported by the disclosure. *Ex parte Tao Xie*, 2008 WL 5232784, *2 (B.P.A.I. 2008). Disclosure may be implicit in the written description if it would have been clear to one of ordinary skill that the inventor possessed the limitation as part of his invention. *Id*. (specification must unambiguously describe all limitations); *see In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976) (holding that in order to find adequate support it is necessary that "persons of ordinary skill in the art will recognize from the disclosure that [the inventors'] invented processes include[ed] those limitations"); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998) ("In order for a disclosure to be inherent … the missing descriptive matter must necessarily be present in the [original] application's specification such that one skilled in the art would recognize such a disclosure.").

"Specification does not does not indicate to avoid zirconium or that the particular 'P2O5-ZrO2-SiO2' particles should not be included."). The mere non-disclosure of a plating step between the first and second cryopreservations in Example 1 does not "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citation omitted).

Far from prohibiting plating, the specification elsewhere expressly encouraged the use of plating. (JX 1 ('929 patent) col. 13 lns. 25-43 (disclosing a process for plating thawed hepatocytes to enhance viability).) That teaching squarely contradicts any suggestion that one of ordinary skill in the art would conclude from the specification that the patent included a **prohibition** against plating.

LTC's evidence that one of ordinary skill in the art would find no support for the "no plating" requirement and "density gradient step" prohibition remains uncontested. LTC has raised more than a substantial question about the inadequacy of the written description; it has, in fact, shown the invalidity of the patent based on its inadequate description.

2. The '929 Patent is Invalid for Obviousness.

LTC established that the asserted claims are merely "[t]he combination of familiar elements according to known methods" that "yield predictable results" and, therefore, are obvious over the prior art. *See KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 416-17 (2007). It is undisputed that every step of the Claim 1 method – cryopreserving hepatocytes, thawing cryopreserved hepatocytes, and density gradient fractionation – was well known in the prior art.

The inventor, Daniel Dryden, admitted that each of these steps was well established in the art by April of 2005, and that he did nothing new or different with respect to any of steps. (DX 7 (Dryden Dep.) at 22:1-5, 24:14-25:13, 26:7-28:23, 32:20-33:12, 59:12-65:16.) Celsis's expert, Dr. Strom, likewise admitted that use of density fractionation to separate viable and non-viable

cells was "well established to everyone in this field," and a person of ordinary skill in the art would have known and fully expected that the viability of cryopreserved hepatocytes could be substantially enhanced with density gradient fractionation. (Tr. at 627:22 – 628:11.) According to Dr. Strom, "[a] person of ordinary skill would believe that you could get *very high viability* using a Percoll separation … and everybody's going to expect this as the result." (Tr. at 627:11-15) (emphasis added).) Drs. Gupta and Li also confirmed that each step of the Claim 1 method was well known before the '929 patent application was filed. (JX 34 at ¶¶ 33-37; Tr. at 360:16-361:20, 388:1-391:21, 398:25-399:17, 401:18-403:5; JX 9 at ¶¶ 5–6.)

Neither *de Sousa* nor *Ulrich* was cited to or considered by the Examiner. Each of them separately, however, was material, since each was much stronger prior art than was *Ostrowska*, the only reference asserted by the Examiner to show a reasonable expectation of high viability. For example, Celsis argued during prosecution that *Ostrowska* showed less than 70% viability after a single freeze/thaw cycle and Percoll purification enhancement. (JX 68 at 9.)

In sharp contrast, *Ulrich* showed hepatocyte preparations that had viabilities of 75% to 85% *before* enhancement by Percoll purification. (JX 43 at 32.) Since a Percoll purification would have been expected to further enhance these viabilities to above 90%, this reference gives rise to very different expectations of viability after a subsequent purification and a second freeze/thaw cycle than given by *Ostrowska*. An even more striking contrast is evidenced by *de Sousa*, because it showed human hepatocytes that had been through a freeze/thaw cycle and had ended up with a viability after Percoll of 92.5%. (JX 48 at 354, Table 1.)

Celsis attempts to argue that viability numbers are irrelevant and that one cannot apply math to the viability numbers because the problem is one of biology, not math. This, however, is

a significant change of course for Celsis, which validated the mathematical approach to viabilities when it tried to get its patent issued during prosecution:

> Moreover, Ostrowska discloses an average viability of less than 70% after only one round of cryopreservation, with the drop in viability being an average of 15% in one freeze-thaw cycle. (*See* Ostrowska at 59). If one were to cryopreserve Ostrowska's hepatocytes a second time, the viability would likely drop another 15%, reducing the viability to approximately 50% at most. (Dryden Declaration at ¶ 7).

(JX 68 at 9-10 (citations in original).)

Using similar methodology, *Ulrich* and *de Sousa* would have yielded expected viabilities after the second thaw (and without a density gradient step following the second thaw) of 75% to 85% for *Ulrich* and 78.8% for *de Sousa*. By applying Celsis's methodology to *Ulrich* and *de Sousa*, it becomes clear that one of ordinary skill in the art would have reasonably expected to be able to freeze and thaw hepatocytes twice and have viabilities above 70%, without needing to do a Percoll purification after the second thaw. Celsis's attempt to now disown its own prosecution argumentation should be repudiated.

Moreover, the 2002 *Malhi* article, also not before the Examiner, disclosed multi-cryopreservation of hepatocytes with viabilities exceeding 70%:

> It was noteworthy that our cells were highly viable following release from culture dishes and serial subpassaging, including, **after repeated cryopreservation, >80% of cells attaching to culture dishes following thawing and producing long-term cultures** (Table 3).

(JX 47 at 2684 (emphasis added).)

According to Dr. Gupta, a person of ordinary skill in the art would have understood from *Malhi* that human hepatocyte cells could be repeatedly cryopreserved and thawed with maintenance of high viabilities. (Tr. at 460:12-20; JX 34 at ¶ 28.) Accordingly, the Examiner would have certainly considered *Malhi* highly relevant to the patentability of the claimed methods.

Malhi taught precisely what Celsis repeatedly argued was missing in the prior art – hepatocytes subjected to multiple freeze-thaw cycles. Celsis had argued, for example: "There is simply *not one single reference or combination of references* that show(s) more than one round of freezing and thawing hepatocytes, so as to maintain high viability. Moreover, there is not even one single reference that even contemplates multi-cryopreserving hepatocytes as a desirable technique." (JX 65 at 12) (emphasis added).); "There are simply no teachings, suggestions or motivation found in the cited references to multi-cryopreserve hepatocytes." (JX 63 at 12); "[P]rior to Applicants' invention, no one had been able to successfully multi-cryopreserve hepatocytes…. Nor has anyone besides Applicant been able to do so." (JX 63 at 15.)

If the Examiner had had the benefit of *Malhi,* this paper would have confirmed her conclusion that the multi-cryopreservation of hepatocytes was obvious. Indeed, as Celsis concedes in its reply brief, *Malhi* "would have admittedly altered the dynamic of the obviousness case previously considered by the Patent Office." (Reply at 20.) *Malhi*, in combination with either *de Sousa* or *Ulrich*, raises a substantial question regarding the obviousness of the '929 patent and renders preliminary injunctive relief inappropriate.

At the hearing, Celsis made a meritless argument that *Malhi* is irrelevant. Celsis alleged that *Malhi* is of no import because *fetal* hepatocytes, not adult cells, were used. Yet, as Dr. Strom conceded (Tr. at 255:2-8), Celsis's claims are not limited to adult hepatocytes. Celsis also argued that *Malhi* plated the hepatocyte cells between cryopreservations, whereas the claims prohibit plating. (Reply at 20.) This argument likewise lacks merit: the specification *does not restrict plating* of the cells between cryopreservations. (*See* JX 1 ('929 patent) col. 13 lns. 25-43.) Therefore, *Malhi* bears directly upon the method disclosed by Celsis's patent application.[8]

[8] This argument applies with equal force to claims 1 and 10 of the '929 patent. Those claims both claim "multi-cryopreserved hepatocyte preparation" having greater than 70% viability after the last thaw. (JX 1 ('929 patent).)

No testimony offered by Celsis contradicted the basic facts of this case: Celsis's claimed method merely arranged old elements, each performing a known function, to achieve a predictable result. Celsis and Dr. Strom do not dispute that the methods used by Celsis were well known in the scientific community. (*See* Tr. at 627:5-628:11 (Dr. Strom describes density gradient fractionation using a Percoll solution as "a common technique" that "will enhance viability. It's well established. All of us in the art understand that.").) The only supposed novelty, as repeatedly argued to the Examiner, was that an extra freeze-thaw would yield hepatocytes with viability greater than 70%. But even this result was fully expected by one skilled in the art in April 2005. Consequently, substantial questions exist about the obviousness of Celsis's claimed invention such that a preliminary injunction should not issue.

C. THERE IS A SUBSTANTIAL QUESTION REGARDING THE ENFORCEABILITY OF THE '929 PATENT.

Celsis has engaged in inequitable conduct because (1) with intent to mislead or deceive the Examiner, (2) it failed to disclose material information to the PTO during prosecution. Celsis's inequitable conduct renders the '929 patent unenforceable. *See Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006).

That Celsis acted with intent to mislead or deceive the Examiner is undisputed. Celsis has failed to offer any other explanation for its conduct in its briefing or testimony before this Court. Indeed, when directly questioned by the Court during closing argument, Celsis failed to suggest any alternative explanation for its conduct. (Tr. at 792:12-793:5.) *See Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1313 (Fed. Cir. 2008) (finding inequitable conduct where there was no testimony to explain the failure to disclose material information).

Consequently, both claims are obvious in light of *Malhi*, *de Sousa*, and *Ulrich*. The use of cryopreserved hepatocytes to study the effect of xenobiotics upon hepatocytes is obvious in light of, among other prior art, *Shibata*. (JX 29.)

In fact, the only defense offered by Celsis is that the withheld information was merely cumulative and, therefore, not material. However, the materiality of the information Celsis failed to disclose to the PTO is clear: the text and references deleted from *Terry* directly contradict Celsis's fundamental argument about hepatocyte viability and undermine the Examiner's final conclusion. That the viability of hepatocytes after cryopreservation was the key metric urged by Celsis throughout the patent process is evident from its repeated statements to that effect during prosecution, including, for example: "[I]t is well known that even singly cryopreserved hepatocytes exhibit many problems upon thawing." (JX 65 at 13); "[R]esearchers were skeptical that even a singly-cryopreserved hepatocyte preparation could be made, let alone the present invention." (JX 68 at 12; s*ee also* JX 68 at 8, 10; JX 73 at 14, 15; JX 75 at 14.)

However, in its quotation of *Terry* (which otherwise seemed to support its position), Celsis intentionally cut the following critical phrases and associated citations:

> With human hepatocytes this decrease [in the trypan blue membrane integrity assay] can be a 20-30% drop after cryopreservation [20, 29, 33, 67]. **Some authors, however, have found that human hepatocyte viability can be maintained after cryopreservation [17, 26, 96].**
>
> A common observation is that, **although hepatocyte viability may remain comparable to that of fresh hepatocytes after cryopreservation,** a much smaller percentage will be able to attach to the culture substrate (usually collagen) [28,100].

(JX 12 at 154 (emphasis added).)

The *de Sousa* and *Ulrich* papers cited in the excised statements as references 26 and 96 disclose very high hepatocyte viability after cryopreservation; yet neither of these references was disclosed to the Examiner. Had the Examiner been aware of this highly material information, it is unlikely she would have allowed Celsis's claims. Indeed, the claims were only allowed because she understood from Celsis's representations that the prior art did *not* disclose methods of freezing and thawing hepatocytes having high viability. In her Allowance, the Examiner stated:

> The prior art teaches that hepatocytes are extremely difficult to work with and that it is extremely difficult to maintain a sufficient level of viability of hepatocytes ***during even one round of cryopreservation and thawing***.

(JX 79 at 2 (Notice of Allowability) (emphasis added).)

It is clear that Celsis intentionally and deceptively excised information that contradicted its arguments.[9] Specifically, it is clear that Celsis hid this material in order to deceive the Examiner into believing that a skilled artisan would have expected very poor viability of hepatocytes after even a single cryopreservation. Celsis understood that its only chance of getting a patent to issue was to convince the Examiner that this "fact" was accepted by one of skill in the art. *Terry*, as published, stood in the way of this objective. *Terry*, as quoted, did not.

In addition to its deletions and omissions from *Terry*, Celsis also engaged in inequitable conduct by submitting the misleading Dryden experiment data. The June 22, 2009 Dryden Declaration described three experiments, denominated A (individual single-cryopreserved hepatocyte preparations), B (individual multi-cryopreserved hepatocyte preparations), and C (pooled multi-cryopreserved preparations). (JX 76.) Because the Declaration was submitted to overcome prior art rejections of some pending claims, the Declaration was highly material. It was misleading for at least two reasons.[10]

First, Dryden skewed the results of his experiments by starting with substandard cells, so that viability was below the 70% benchmark of the patent upon a first thaw. (DX 7 at 193: 1-16.)[11] As a result, Dryden reported viabilities of 61% for the single-cryopreserved cells,

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[9] Celsis has suggested that even though it attempted to hide the excised quotes from the Examiner, she must have read *Terry* and been aware of the Celsis omissions because she subsequently cited *Terry* for a different proposition. (Tr. 798:5-9.) However, the fact remains that the deleted material in *Terry* directly contradicted the Examiner's Reasons for Allowance. Had she read the deleted material, she certainly would have addressed it on the record.

[10] In his deposition, Dryden claimed that the raw data supporting this Declaration was never entered in a laboratory notebook or otherwise preserved. (DX 7 (Dryden Dep.) at 191:21-192:24.) Accordingly, there is no way to ascertain if the experiments contained additional flaws.

[11] In his deposition, Dryden admitted that he reserved high viability hepatocytes for sale to Celsis customers. (DX 7 at 193:12-16.)

and 77% to 85% for cells that had been multi-cryopreserved. (JX 76 at ¶ 6.) In its submittal to the Examiner, Celsis argued:

> Further, as disclosed in the Dryden Declaration, the multi-cryopreserved hepatocyte preparation of the present invention has a significantly higher viability and metabolic activity when compared with a singly-cryopreserved hepatocyte preparation, and an unpooled but multi-cryopreserved preparation.
>
> * * *
>
> This data demonstrates that the cell product prepared by the present invention is a substantially different product than a singly-cryopreserved product, as described by Ostrowska.

(JX 75 at 14-15.) Celsis wanted the Examiner to conclude that the differences in viability were due to its multi-cryopreservation technique.

In fact, the "results" were pre-ordained in its favor. First, the low viability reported in the single-cryopreserved cells was a direct result of Dryden's intentional use of low-viability cells in the experiment.

Second, Celsis did not disclose that the three experimental preparations were made using different protocols with respect to Percoll purification. In his Declaration, Dryden directly compared the viability results in Experiments A and B:

> In Experiment A, the singly-cryopreserved hepatocyte cultures, or Individual Donors, had an average viability of 61%. The metabolic activities of these cultures are shown in Exhibit A. In Experiment B, the LiverPooled individual cultures ***demonstrated an average viability and metabolic activities that were, in all cases, significantly higher than the singly-cryopreserved cultures*** . . . .

(JX 76 at ¶6 (emphasis added).) This argument was repeated in the accompanying Amendment. (JX 75 at 14.) What Dryden knew and did not disclose was that the cells of Experiment A had not been subjected to a Percoll density gradient step, but those of Experiment B had been in order to enhance viability. (DX 7 at 182:18–183:2.) These different methods completely account for the difference between single- and multi-cryopreserved cells. Had this information

been disclosed, this experiment would have demonstrated only one thing: the well-known fact that Percoll enhances hepatocyte viability.

But for Celsis's misrepresentations of prior art and its experiments, the Examiner likely would not have granted the '929 patent. Celsis's inequitable conduct should bar its enforcement of the '929 patent. Because LTC has raised serious issues at this hearing related to Celsis's inequitable conduct, no preliminary injunction should issue.

D. THE EQUITIES WEIGH AGAINST GRANTING CELSIS'S PRELIMINARY INJUNCTION.

The testimony of Celsis regarding its alleged damages demonstrates that its claimed harms are monetary in nature. In an effort to prove "irreparable damages," Celsis presented the testimony of Mark Peterson, who admitted that he routinely quantifies the types of damages that Celsis alleges. (Tr. at 329:13.)

If the preliminary injunction is denied, Celsis will still have the opportunity to recover damages at trial if it can establish a breach of its patent. On the other hand, if a preliminary injunction is granted, it will dramatically shift the status quo and cause substantial and irreparable harm to LTC. CellzDirect will have to shut down much of its operations. This forced standstill until the end of a yet-to-be scheduled trial could be the death knell for CellzDirect, and cannot be adequately addressed through the posting of a bond.

In addition, the public interest militates against an injunction. LTC's pooled human hepatocyte products are used in important pharmaceutical research and development. Barring the production and sale of these hepatocytes will harm research in progress by forcing a change in protocols or even abandonment of research, and will decrease the diversity of hepatocyte cell lines available to researchers.

E. ANY PRELIMINARY INJUNCTION MUST BE APPROPRIATE IN SCOPE.

The Court should not grant the extraordinary relief of a preliminary injunction. However, if the Court grants Celsis's motion, the scope of the preliminary injunction must be no broader than the claims of the '929 patent.[12]

The '929 patent recites only **method claims**; thus, the injunction should be limited to the specific methods recited in the '929 patent as further described below.[13] *See Eli Lilly and Co. v. Medtronic, Inc.*, 915 F.2d 670, 674 (Fed. Cir. 1990) ("An injunction is only proper to the extent it is to prevent the violation of any right secured by patent."); *Joy Tech. v. Flakt, Inc.*, 6 F.3d 770, 775-76 (Fed. Cir. 1993) (in a case involving a method claim, a preliminary injunction against sale of product was improper).

Furthermore, LTC cannot be prevented from selling, offering for sale, or exporting or importing pooled cryopreserved human hepatocyte products made before October 20, 2009, when the patent issued. *See Mycogen Plant Sci., Inc. v. Monsanto Co.*, 252 F.3d 1306, 1318-19 (Fed. Cir. 2001) (Alleged infringer "do[es] not infringe a process patent if they practice the process before the beginning of the patent term, even if they sell the products of the process during the term of the patent"), *vacated on other grounds*, 535 U.S. 1109 (2002). As a matter of law, those products could not have been made by an infringing process because the patent had not yet issued. *See* 35 U.S.C. § 271(a); *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352,

[12] Should the Court orally issue its decision, LTC respectfully requests advance notice in order to appear.

[13] The TRO, to which LTC objected, improperly restrained LTC from "selling, offering to sell, making, using or exporting any of their pooled multi-cryopreserved hepatocyte **products**. . ." (Mem. Op. and Order, July 15, 2010 (Dkt. No. 43) at 2 (emphasis added).) This is overbroad because the '929 patent does not recite any product claims.

1360 (Fed. Cir. 2007) (stating that a method claim is not infringed if one or more steps are practiced before the issuance of the patent).[14]

Furthermore, the scope of any injunction must be limited to a method of making twice frozen and twice thawed hepatocytes[15] prepared by fractionation in a density gradient wherein the fractionation is based on no property other than density[16] and further are not put onto a plate for any purpose between the first and second cryopreservations[17] and are not subjected to a density gradient separation step after the second thaw.[18]

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[14] Even if Celsis had shown it was entitled to "provisional rights" under 35 U.S.C. § 154(d), which it has not, such provisional rights would only entitle Celsis to damages for pre-issuance activity, not an injunction. 35 U.S.C. § 154(d)(1).

[15] Claim 1 is directed to a method for making a "preparation of multi-cryopreserved hepatocytes." Asserted claim 10 is directed to a use of "a multi-cryopreserved hepatocyte preparation." The preparation is defined in the specification as "hepatocytes that have been frozen and **thawed at least two times**." JX 1 ('929 patent) col. 4 ln. 18-20 (emphasis added).) Consistent with that definition and the plain language of the claims, Dr. Strom testified that "one is required to thaw the desired preparation of multi-cryopreserved hepatocytes for a second time to practice claim 1" of the '929 patent. (Tr. at 210:4-15.) Accordingly, a preliminary injunction can only enjoin the manufacture (as described in claim 1) and use (as described in claim 10) of twice frozen and twice thawed hepatocytes (as further limited below).

[16] Claim 1 is directed to a method for preparing hepatocytes that have been twice frozen and twice thawed, wherein a density gradient fractionation step is employed between the first and second cryopreservations to separate non-viable from viable hepatocytes. Similarly, claim 10 is directed to a particular use of hepatocytes prepared essentially by the method of Claim 1. "Density gradient fractionation" is fractionation in a density gradient wherein the fractionation is based on no property other than density. Dr. Strom admitted that the specification does not disclose separation of viable and non-viable hepatocytes on the basis of any property other than density (Tr. at 260:14-261:1) and that there are numerous unclaimed separation techniques other than the claimed density gradient fractionation separation technique, including elutriation and plastic adherence. (*Id*. at 250:16-252:10, 258:17-259:18.) Consequently, the injunction cannot restrict LTC from making or using pooled cryopreserved human hepatocyte products prepared by techniques (such as elutriation and plastic adherence) that separate viable from non-viable hepatocytes on the basis of properties other than density alone, or from selling, offering for sale and exporting/importing products made by such techniques. Any injunction order must carve out techniques that do not employ a density gradient, such as techniques that separate viable and non-viable hepatocytes on the basis of any property other than density.

[17] Claims 1 and 10 each recite that the hepatocytes "are not plated between the first and second cryopreservations." Dr. Strom testified that one of ordinary skill in the art would understand "plating" to "mean putting the hepatocytes into a culture plate and maybe to allow them to attach, but they wouldn't have to attach, but just simply putting them into a culture plate for some purpose." (Tr. at 189:6-11.) Any injunction must be crafted so as to not enjoin a method wherein the hepatocytes are put into a plate for any purpose between the first and second cryopreservations.

[18] Claims 1 and 10 each require that the hepatocyte preparation achieves the recited viability "without requiring a density gradient step" after the second thaw. Accordingly, a preliminary injunction should not enjoin LTC from utilizing a method in which such a step is required to achieve hepatocyte viability exceeding 70%.

F. THE COURT SHOULD STAY ENFORCEMENT OF ANY PRELIMINARY INJUNCTION PENDING APPEAL.

Furthermore, if the Court enters a preliminary injunction, LTC respectfully requests that the Court stay enforcement of the injunction and stay all trial court proceedings pending the outcome of an appeal to the Federal Circuit. Fed. R. Civ. P. 62. The four factors to be considered in issuing a stay pending appeal are: "(1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies." *Hilton v. Braunskill*, 481 U.S. 770, 776, 107 S.Ct. 2113, 95 L.Ed.2d. 724 (1987). As explained herein, LTC has a significant probability of success on the merits and, as Mr. Hunkeler testified, LTC has and will continue to suffer irreparable harm as a consequence of shutting down a part of its business and related product development and loss of long-term relationships with customers and their business. (JX 8 (Supp. Hunkeler Decl.) ¶4.) Furthermore, a short stay will not substantially injure Celsis because any alleged short-term harm is compensable monetarily. A stay is "in the public interest," and of particular interest to LTC's customers that rely on LTC's pooled cryopreserved human hepatocytes to develop vital and life-saving drugs and therapies for the public. (*Id*. ¶5.)

III. CONCLUSION

Celsis is not entitled to the extraordinary remedy of a preliminary injunction because it has not shown a likelihood of success on the merits. LTC has raised substantial questions regarding infringement, validity, and enforceability of the '929 patent.

LTC has not infringed the '929 patent under a proper construction of "density gradient fractionation." Furthermore, there are substantial questions regarding validity of the patent,

which should be held invalid both for lack of written description and for obviousness. The '929 patent is also not enforceable because of Celsis's inequitable conduct: Celsis overcame the Examiner's obviousness rejections only by intentionally and repeatedly misleading the Examiner. Finally, Celsis cannot meet the other requirements for injunctive relief because it has not suffered irreparable harm, and the balance of hardships and the public interest favor LTC.

Celsis's motion for preliminary injunction should be denied. If, however, the Court decides to enter a preliminary injunction, it should be carefully limited in scope as described above, and the Court should stay enforcement pending an appeal.

DATED this 23rd day of August, 2010.

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CERTIFICATE OF SERVICE

I hereby certify that on the 23rd day of August, 2010, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF system which will send notification of such filing to the following:

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